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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/589,285	06/08/00	YU G	PF343P3C4

022195
HUMAN GENOME SCIENCES INC
9410 KEY WEST AVENUE
ROCKVILLE MD 20850

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EXAMINER	
PRASAD,S	
ART UNIT	PAPER NUMBER
1646	8

DATE MAILED: 11/06/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/589,285	Applicant(s) Yu et al.	
	Examiner Sarada C Prasad	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 20 August 2001 .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,17,19 and 26-274 is/are pending in the application.

4a) Of the above claim(s) 1,17,19 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 26-274 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Detailed Action

1. Applicant's election with traverse of Group IV in Paper No. 7 (8/20/01) is acknowledged. Original claims 2-16, 18 and 20-25 have been cancelled and new claims 26-274 have been added. Currently, claims 1,17, 19, and 26-274 are pending.

The traversal is on the ground(s) that a search of the polynucleotide claims would clearly provide useful information for the polypeptide claims and a search of the polypeptide claims, as a matter of routine, would include a search for antibodies, and hence restriction of original claims 1-25 to Groups I, II, III is not proper. This is not found persuasive because the inventions of Groups I, II and III, directed to polynucleotide, polypeptide, and antibodies are distinct as noted in the last Office Action, and as shown by the distinctness described therein. Applicant's attention is directed to MPEP 806.05. Contrary to applicants' assertion that any search of the prior art in regard to Group I would reveal whether any prior art exists as to the other inventions of Groups II and III, the search is in fact directed to references which would render the invention obvious, as well as references directed to anticipation of the invention, and therefore requires a focussed search of relevant literature in many different areas of subject matter. Furthermore, divergent classification of the three Groups of inventions I-III has been an additional criterion for the restriction of the claims 1-26 into three distinct inventions.

The requirement is still deemed proper and is therefore made FINAL.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the

application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Currently, claims 26-274 are under consideration.

Specification

2a. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

2b. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. A suggested title would be 'A method of treatment of immune system-related disorders with neutrokine-α'.

Claim Rejections - 35 USC § 112-First paragraph-Scope of enablement

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3a. Claims 26-274 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of stimulation of B-lymphocyte proliferation comprising administering to an individual, an effective amount of a full length protein consisting of an amino acid sequence of SEQ ID No.2, but does not reasonably provide enablement for a method of treating 'an immune system disease or disorder' or 'an autoimmune disease or disorder' or 'immunodeficiency' or for stimulating B-lymphocyte proliferation, comprising administering to an individual a therapeutically effective amount of 'any' fragments, derivatives, fusion peptides, or variants, or fusion peptides of variants of SEQ ID No.2. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Issues that are addressed in the rejection:

There are two different issues of scope of enablement in this rejection:

(a) stimulation of B-lymphocyte proliferation with full length polypeptide of SEQ ID No.2, and/or all of the contemplated fragments, fusion peptides and derivatives of SEQ ID No. 2; and

(b) treatment of all immune system diseases or disorders, autoimmune diseases or disorders, or immunodeficiencies by administering full length polypeptide of SEQ ID No.2, and/or all of the contemplated fragments, fusion peptides and derivatives of SEQ ID No. 2.

What does specification set forth:

The specification sets forth general methods and compositions for treatment of immune system related disorders (specification page 310-366). General methods of making the peptides of SEQ ID No. 2 for use as therapeutics is also disclosed in the specification (pages 31-231). In particular, methods of lymphocyte proliferation/activation by administering SEQ ID No.2 have been disclosed in Examples 6, and 7 (pages 412-425).

The specification is only enabled for B-lymphocyte proliferation with the full length polypeptide of SEQ ID No.2. The specification is not enabled for either B-lymphocyte proliferation, or treatment of any of the said diseases using fragments, derivatives, or peptides of SEQ ID No.2.

However, recitation of a method of treatment of immune system diseases or disorders including all of the autoimmune diseases or disorders, immunodeficiency diseases, comprising administering a therapeutically effective amount of

(i) peptide fragments of SEQ ID No. 2 with amino acid residues n-285, where n is an integer in the range of 2-190; or 1-m where m is an integer in the range of 274-284; or peptides with amino acid residues n-m of SEQ ID No.2, where n is an integer in the range of 2-190, and m is an integer in the range of 274-284;

(ii) fusion peptides comprising a first amino acid sequence that is 95% or more identical to a second amino acid sequence consisting of either peptide fragments of SEQ ID No. 2 with amino acid residues n-285, where n is an integer in the range of 2-190; or 1-m where m is an integer in the range of 274-284; or peptides with amino acid residues n-m of SEQ ID No.2, where n is an integer in the range of 2-190, and m is an integer in the range of 274-284;

(iii) a protein consisting of amino acid sequence of 134-285 of SEQ ID NO.2, or a first amino acid sequence which is 90% or more identical to a second amino acid sequence consisting of residues 134-285 of SEQ ID No.2, wherein the polypeptide having the first amino acid sequence modulates lymphocyte proliferation;

(iv) the amino acid sequence of an anima terminal deletion protein mutant of the full length protein encoded by the cDNA contained in ATCC deposit number 97768, wherein said amino terminal deletion protein mutant excludes up to 190 residues from the amino terminus of said full length protein encoded by the cDNA contained in ATCC deposit number 97768;

(v) the amino acid sequence of a carboxy terminal deletion protein mutant of the full length protein encoded by the cDNA contained in ATCC deposit number 97768, wherein said

carboxy terminal deletion mutant excludes up to 11 amino acid residues from the carboxy terminus of said full length protein encoded by the cDNA contained in ATCC deposit number 97768;

(vi) the amino acid sequence of an amino and carboxy terminal deletion protein mutant of the full length protein encoded by the cDNA contained in ATCC deposit number 97768, wherein said amino and carboxy terminal deletion protein mutant excludes up top 190 amino acids from the amino terminus and up to 11 residues from the carboxy terminus of said full length protein encoded by the cDNA contained in ATCC deposit number 97768, wherein the peptide sequence modulates lymphocyte proliferation;

(vii) a protein consisting of a first amino acid sequence that is 95% or more identical to a second amino acid sequence consisting of/comprising the amino acid sequence of an amino terminal deletion protein mutant of the full length protein encoded by the cDNA contained in ATCC Deposit number 97768, wherein said amino-terminal deletion protein mutant excludes up to 133 amino acid residues from the amino terminus of said full length protein encoded by the cDNA contained in ATCC deposit Number 97768, wherein the polypeptide having said first amino acid sequence modulates lymphocyte proliferation;

or a method of stimulating leukocyte activation or proliferation comprising administering to an individual, a therapeutically effective amount of

(viii) amino acid sequence with residues n-285 of SEQ ID No. 2, where n is an integer in the range of 2-190, or 1-m where m is an integer in the range of 274-284, or an amino acid sequence with residues n-m of SEQ ID No.2 where n is an integer in the range of 2-190 and m is

an integer in the range of 274-284, where that polypeptide having said amino acid sequence modulates lymphocyte proliferation;

(ix) protein comprising a first amino acid sequence that is 95% or more identical to a second amino acid sequence selected from the group consisting of amino acid sequence with residues n-285 of SEQ ID No. 2, where n is an integer in the range of 2-190, or 1-m where m is an integer in the range of 274-284, or an amino acid sequence with residues n-m of SEQ ID No.2 where n is an integer in the range of 2-190 and m is an integer in the range of 274-284, where that polypeptide having said amino acid sequence modulates lymphocyte proliferation;

(x) a protein consisting of an amino acid sequence of amino acid residues 134-285 of SEQ ID No.2;

or a method of enhancing host defenses against infection comprising administering to an individual, a therapeutically effective amount of

(xi) amino acid sequence with residues n-285 of SEQ ID No. 2, where n is an integer in the range of 2-190, or 1-m where m is an integer in the range of 274-284, or an amino acid sequence with residues n-m of SEQ ID No.2 where n is an integer in the range of 2-190 and m is an integer in the range of 274-284, where that polypeptide having said amino acid sequence modulates lymphocyte proliferation;

(xii) protein comprising a first amino acid sequence that is 95% or more identical to a second amino acid sequence selected from the group consisting of amino acid sequence with residues n-285 of SEQ ID No. 2, where n is an integer in the range of 2-190, or 1-m where m is an integer in the range of 274-284, or an amino acid sequence with residues n-m of SEQ ID No.2

where n is an integer in the range of 2-190, and m is an integer in the range of 274-284, where that polypeptide having said amino acid sequence modulates lymphocyte proliferation;

(xiii) a protein consisting of an amino acid sequence of amino acid residues 134-285 of SEQ ID No. 2,

in claims 26, 39, 52, 62, 72, 82, 89, 98, 107, 126, 140, 154, 170, 186, 199, 212, 221, 230, 236, 250, 264 is extremely broad.

Analyses of why the instant claims are rejected based on their broad scope:

Diversity of diseases to be treated:

The disclosure has provided evidence for B-lymphocyte proliferation by administering full length polypeptide of SEQ ID No.2 but failed to compare the potential of full length polypeptide with any of the contemplated peptides, either for B-lymphocyte proliferataion, or for contemplated treatment of any of the numerous diseases that the claim language encompasses. There is no guidance for one of skill in the art for selection of patient population for treatment, and what are the particular symptoms to alleviate other than stimulate B-lymphocyte proliferation. The limited guidance provided is insufficient with the only one response (lymphocyte activation) observed to be affected by the instant SEQ ID No. 2. State of the art dictates that for treatment of any particular disease, the expected outcome is relief of symptoms, which has not been provided in the specification. The specification is not enabled for treatment of any of the immune system disease or disorder, autoimmune disease, or disorder, or immunodeficiency because there is no guidance provided for treatment of any of the said diseases comprising administering either full length polypeptide of SEQ ID No.2, or fragments, or portions, or fusion peptides of SEQ ID No.2. It is essential to have guidance for the diseases to

be treated because the expected relief of symptoms depends on the nature of disease symptoms. Furthermore, recitation of treatment of '....disorder....' includes any combination of symptoms that might or might not have been classified as belonging to any one disease in particular. In the absence of recitation of symptoms, or identification/diagnosis of specific immune system related disorders to be treated with the instant polypeptide derivatives of SEQ ID NO. 2, the claim language can be interpreted to include 'treatment of all of the diseases' contemplated, which is only mere speculation and not true. This is asking for license to perform further experimentation. Therefore, it is not feasible for one of skill in the art to treat unnamed immune system disease, or autoimmune disease, or disorder, or immunodeficiency as recited in the instant claims.

Diversity of neutrokine-α polypeptides for use as agents for treatment:

Recitation of administering various fragments, derivatives, fusion peptides, variants of SEQ NO. 2 for treatment of immune system diseases in the claim language includes all of the derivatives contemplated, which is only mere speculation and not true. No guidance is provided to enable one of skill in the art to test each of these numerous variants of the instant SEQ ID No.2 to achieve therapeutic benefit in various unnamed immune system related disorders. The disclosure fails to provide any details of having used the polypeptides generated with N-terminal and C-terminal deletion mutants or fusion peptides. Particularly, the sequence 134-285 of SEQ ID No.2, much emphasized in the claims as being equivalent to full length polypeptide of SEQ ID No.2, has not been disclosed to have been used for any of the examples either to achieve B-lymphocyte stimulation, or in the treatment of graft vs. host decease, or in the gene therapy example provided in the specification. Guidance is also not provided for a skilled artisan if there is any one variant that is 90% or 95% identical to SEQ ID No. 2 that has been used to make the

fusion peptide, and used for the intended therapeutic purposes. State of the art dictates that not all regions of SEQID NO.2 can have the structural and functional features of neutrokine-α, or exhibit characteristic properties of stimulating B-lymphocyte proliferation. It is also mentioned in the specification that in spite of the increased B-lymphocyte numbers in response to the administration of neutrokine-α, an increase in IgG has not been noted (page 417, 1st para, last 2 lines). The specification failed to explain the significance of this observation. The Applicants are attempting to determine which of the amino acid residues at C- or N-terminus are dispensable, and which are the ones that are important for the lymphocyte proliferating activity or for enhancing host defenses. It is not feasible for one of skill in the art to treat an individual with unnamed immune system related disease or disorder with any of the several contemplated fragments covering different portions of SEQ ID No. 2.

See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. Given the breadth of claims reciting a method of treating an immune system disease comprising administering fragments, derivatives, fusion peptides, variant polypeptides, or epitope bearing antigenic peptides of neurtrokine-alpha; in light of the predictability of the art that treatment with uncharacterized polypeptides with partial identities to SEQ ID NO. 2 does not result in lymphocyte proliferation, or enhancement of host defenses; as determined by the lack of working examples showing that any of the contemplated fragments, fusion peptides or variants possess expected activity characteristic of neutrokine-α, state of the art suggesting how guidance is needed for a skilled artisan to treat each specific disease in a specific manner, it

would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claims 27-38, 40-51, 53-61, 73-81, 83-88, 90-97, 99-106, 108-125, 141-153, 155-169, 171-185, 187-198, 200-211, 213-220, 231-235, 237-249, 251-263, 265-274 are rejected insofar as they depend on claims 26, 39, 52, 62, 72, 82, 89, 98, 107, 126, 140, 154, 170, 186, 199, 212, 221, 230, 236, 250, 264.

Claim Rejections - 35 USC § 112-written description

3b. Claims 26-274 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification sets forth a polypeptide of SEQ ID No. 2 representing neutrokine-α, a member of the TNF superfamily (pages 21-22). The disclosure also provides evidence of B-lymphocyte stimulation upon administering an effective amount of full length polypeptide of SEQ ID NO.2 in Example 6 (page 412). However, the written description is not commensurate with variants, derivatives, fragments, fusion peptides of the variants with biological activities characteristic of neutrokine-α, represented by an isolated polypeptide of SEQ ID No. 2, being able to provide adequate support for a method of treating an immune system disease, or disorder, or an autoimmune disease, or disorder, or immunodeficiency.

Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the claimed invention. Therefore, the Applicant is not in possession of the invention as claimed, at the time of filing. This is insufficient to support the

claims as provided by the Revised Written description Guidelines published in the Federal register, vol 66, No.4, pages 1099-1111, Friday January 2001.

Instant disclosure provides an in vitro example of a full length polypeptide of SEQ ID No.2 being able to stimulate proliferation of B-lymphocytes. However, the disclosure fails to provide detailed description directed to a method of treatment of immune system disease or disorder, or autoimmune disease or disorder, or immunodeficiency comprising administering an effective amount of the contemplated variants of the polypeptide of SEQ ID No.2. It is not sufficient to name the claimed variant nucleic acids that can encode for polypeptides comprising 90 or 95% identity to SEQ ID No. 2, or the variant polypeptides without actually generating any of the said variants, and testing them for their ability to achieve therapeutic benefit in patients with the said diseases or disorders. Additionally, none of the proposed 'sequence variants' have been shown to be successfully achieved by the claimed nucleotide changes to SEQ ID No. 2 and tested for their ability to stimulate B-lymphocyte proliferation. Since the disclosure fails to describe successful generation of the said variant polypeptides of SEQ ID NO.2, it can be reasonably concluded that Applicant is not in possession of the claimed treatment methods using the variants, fragments, or derivatives at the time of filing. Therefore, it is not feasible for one of skill in the art to treat unnamed immune system disease, or autoimmune disease, or disorder, or immunodeficiency as recited in the instant claims.

Claims 27-38, 40-51, 53-61, 73-81, 83-88, 90-97, 99-106, 108-125, 141-153, 155-169, 171-185, 187-198, 200-211, 213-220, 231-235, 237-249, 251-263, 265-274 are rejected insofar as they depend on claims 26, 39, 52, 62, 72, 82, 89, 98, 107, 126, 140, 154, 170, 186, 199, 212, 221, 230, 236, 250, 264.

Conclusion

4. No claims are allowed.

Prior art cited: U.S. Patent No. 6,297,367 (Oct 2001) (WO 99/33980 (12/30/1997).

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarada C Prasad whose telephone number is 703-305-1009. The examiner can normally be reached Monday - Friday from 8.00 AM to 4.30 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sarada Prasad, Ph.D.
Examiner
Art Unit 1646
November 2nd, 2001

Yvonne Eyler
YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600